Preface

For optimal effectiveness and safety, medications used to manage both acute and chronic diseases must be administered in dosages carefully tailored according to patient-specific metabolic and excretory functional capacity. Due to variably compromised ability to eliminate certain drugs from the body, patients with kidney disease often present with complex and potentially challenging clinical issues related to adjustment of drug dosages. In these patients, provision of effective and safe pharmacotherapy depends upon not only understanding the pharmacokinetic and pharmacodynamic actions of all prescribed medications but also comprehensive appreciation of each patient’s current clinical status.

In this regard, additional challenges have been recently realized. As of 2009, clinical laboratories in North America and elsewhere are expected to report serum creatinine (SCr) concentrations that are consistent with reference values obtained by isotope dilution mass spectrometry [1]. For most laboratories, this has necessitated recalibration of autoanalyzers. Depending on analyzer manufacturer and model, recalibrated SCr levels are known to be 5–20 % lower than values reported prior to recalibration [2]. Use of recalibrated SCr values with the Cockcroft-Gault equation [3] to calculate estimated creatinine clearance (CrCL) often results in a compounded error leading to a numerically exaggerated estimate of excretory kidney function. If this CrCL value is used as currently recommended by the US Food and Drug Administration [4] for the purpose of determining drug dosages for persons with renal impairment, risk for medication error and drug overdose is increased.

In order to improve the accuracy of measures of kidney function used for staging severity of kidney disease, clinical laboratories now are encouraged to utilize recalibrated SCr concentrations with the 4-variable Modification of Diet in Renal Disease (MDRD) equation [5] or the Chronic Kidney Disease Epidemiological (CKDepi) equation [6] to calculate estimated glomerular filtration rate (eGFR) in mL/min/1.73 m² and to report this number along with the SCr value to clinicians [1, 7]. Although this measure of excretory kidney function often is readily available, it is not fully compatible with FDA-mandated product labeling related to drug dosage adjustment in patients with renal insufficiency. These inconsistencies may lead to further confusion and additional potential errors.

Available resources for adjustment of dosages of drugs in patients with renal insufficiency have been found to be broadly inconsistent and imprecise. A systematic review of dosage recommendations for 100 commonly prescribed medications listed in four widely used compendia found disparities in all of these resources in their recommendations for adjustments of dosage and dosage interval [8]. These differences ranged from minor disagreement regarding suggested dosage amount for a specific medication to divergence as broad and conflicting as no adjustment needed versus contraindicated. The four sources varied in their definitions of renal impairment, and some were found to be qualitative and unclear. In response, authorities conceded that “despite numerous secondary sources of drug dosing information, drug prescribing in renal failure remains imprecise and relies on interpolation, extrapolation, and estimation” [9]. In similar fashion, frequent inconsistencies have been found not only among FDA-approved prescribing information concerning recommended dose adjustments for recently marketed medications but also clinicians’ methods for interpretation and application of these recommendations [10].
Additional resource-related issues may be problematic concerning efforts to provide optimal drug therapy for patients with abnormal or rapidly changing renal function. At least as important as use of inconsistent or discrepant information concerning drug dosing is inability or failure to recognize disparate dosage recommendations. Clinicians should be provided with convenient access to at least two reputable, reliable, and evidence-based sources of information on renal drug dosing, thereby allowing individualized selection of the most relevant regimen based on clinical judgment in light of pharmacological concerns weighted for safety and effectiveness. We sought to satisfy this requirement by compiling a listing of dosing suggestions comprised of official and alternative recommendations.

Methods

Conduct oversight for this project was provided by the Colorado Multiple Institutional Review Board (COMIRB, Protocol № 10-1105). Our objective, based on a review of available resources, was to compile a comprehensive tabular listing of dosage recommendations for patients with compromised renal function.

Information concerning adjustment of selected drug dosages that is compatible with conventional and revised measures of kidney function was obtained from available tertiary, secondary, and primary literature sources. This information was compiled into an alphabetical listing according to the approved generic drug name. Information on drug dosage adjustment was included in the listing if, in the opinion of the authors, such adjustment is necessary.

For all medications included in the listing, FDA-mandated product information was obtained from the package insert. In every instance, careful attempt was made to directly quote or to remain entirely faithful to the actual language and/or meaning within the product information. Alternative dosage adjustment information routinely was obtained from commonly used compendia. Most often, this consisted of GFR-based adjustment recommendations taken from the professional standard Drug Prescribing in Renal Failure [11] (with permission) or any of its various derivatives [12–15]. In most cases, other tertiary [16–21], secondary [22–25], and primary references (or available Internet-based counterparts of these print media) were used. Use of these alternatives often was necessary to supply or, more commonly, to corroborate and/or expand evidence-based dosing information for antimicrobials, newly marketed medications, and drugs used in patients receiving renal replacement therapy. Specialized alternative resources also were used for certain drugs for which information other than that provided in standard compendia was considered preferable.

The primary literature related to drug dosing in kidney disease was reviewed for all renally eliminated medications. In the event that alternative dose recommendations differed from those provided by the manufacturer, information selected and subsequently included in the listing was believed to be the most clinically relevant based on original clinical research and experience. The primary literature also was utilized for all medications for which proprietary dosing information was believed to be inadequate or outmoded and in need of change. This was most often necessary for dose adjustment of medications used for patients receiving renal replacement therapy. Searches for information contained in the primary literature were performed with the US National Library of Medicine’s PubMed indexing system and Elsevier’s Embase using nonproprietary or preferred drug names.

Results

A review of available resources disclosed 349 medications that require or suggest need for dosage adjustment when administered to patients with acute or chronic kidney disease and 769 drug entities that normally do not require dose adjustment for renal impairment. From this review, salient data for each medication was extracted and incorporated into a pre-formatted computer file. This file comprises the listings shown below.
Discussion

To promote effectiveness and minimize possible toxicity, the dosage of certain medications must be adjusted in persons with compromised kidney function. Convenient and comprehensive evidence-based resources are needed to enable consistent application of such adjustments.

Failure to enjoin appropriate dosage adjustments in patients with abnormal or rapidly changing kidney function continues to lead to reports of drug toxicity involving a broad array of renally eliminated medications [26–37]. Better resources clearly are needed to facilitate dose optimization. Means to ensure that patients whose current medications need adjustment are consistently identified also are vitally necessary.

Computerized assessment and consequent-directed recommendations concerning drug dosage have proven capable of improving prescribing patterns. A recent meta-analysis that evaluated 26 controlled comparisons of behavioral prescriber changes and/or health outcomes of patients associated with computerized interventions targeted to affect prescribing documented significant benefit of computerized advice by increasing the initial dose, increasing serum drug concentrations, reducing the time to therapeutic stabilization, reducing the risk of toxic drug levels, and reducing the length of hospital stay [38]. In patients with renal insufficiency, automated clinical decision support (CDS) systems have proven capable of detecting potentially dangerous and costly exposure to excess dosages of antimicrobial and other drugs that occurs frequently despite the intensive monitoring afforded to critically ill patients [39] and those attended in the emergency department [40]. Perhaps most convincing of the value of CDS are data showing that, as compared with pre-implementation figures, implementation of a CDS system was associated with a statistically and clinically significant 39% increase in the fraction of delivered prescriptions for renally eliminated or nephrotoxic medications deemed appropriate according to previously published and/or expert evaluation standards when the system was applied to approximately 100,000 orders for these medications in hospitalized patients with renal insufficiency [41]. CDS systems for renally eliminated medications may be most effective if supplemented with academic detailing [42].

The appendant listing was designed to close some identified gaps in information concerning dosage adjustment of medications eliminated by the kidneys. More importantly, it was composed with the intent that this was to be adapted and used as part of an automated system that would display each patient’s identification, location, and kidney function. Ultimately, the listing is to be used with CDS as described above, thereby enabling provider alerting to need for attention based on determination of specific clinically relevant dosing cusps or breakpoints for prescribed medications with individualized information displayed concerning suggested dose modifications and recommended actions.

This resource listing displays several strengths including alphabetical format, completeness, referencing, and, when available, dosage recommendations based on eGFR [43]. In glaring contrast, it also has significant weaknesses and limitations. First and foremost, we fully understand and appreciate that no single reference related to medication management in patients with kidney disease can provide truly comprehensive, completely accurate, totally unbiased, and thoroughly evidence-based recommendations. Secondly, our information was largely compiled with use of secondary or tertiary data sources with corroboration of the primary literature. Thirdly, alternative dosage adjustment recommendations that include breakpoints set in terms of eGFR often are listed in our information. The authors of the original guidelines in which this standard was established concede that calculated CrCL, an approximation useful in clinical dosimetry, may be used to simulate GFR [44]. These measures of kidney function thusly were considered essentially interchangeable, as demonstrated in earlier clinical investigations [45], and this bias currently persists in the dosing guidelines used as our foremost source of alternative dosage adjustment recommendations [11]. This relationship likely will not hold true if currently available measures of SCr are used to calculate CrCL or if eGFR is not corrected for body surface area in unusually small or large adults. Lastly, other than an
informal acceptability survey of clinicians at the University of Colorado Hospital, the utility of this resource has not been clinically tested. Nonetheless, the appendant listing is believed to satisfy some, if not most, of the dosing information needs of busy clinicians involved in pharmacotherapy for patients with kidney disease.

References


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Renal Pharmacotherapy
Dosage Adjustment of Medications Eliminated by the Kidneys
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